#22/52
8301

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Cederberg et al.
Serial No.	:	08/945,425
Filed	:	October 21, 1997
For	:	ADMINISTRATION OF PHARMACEUTICALS
Examiner	:	R. Desai
Group Art Unit	:	1612

Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION OF CHRISTER CEDERBERG
(Under 37 C.F.R. § 1.132)

Sir:

I, Christer Cederberg, Ph.D., declare as follows:

1. I am a citizen of SWEDEN. I graduated in 1992 from the University of Gothenburg, Sweden, Department of Clinical Pharmacology, with a doctorate in Medical Science.

2. AstraZeneca is the assignee of the referenced application. AstraZeneca R&D Boston, Cambride has employed me from 1999 to the present as the Director of Clinical Pharmacology and Animal Science. From 1979 to 1999, I was employed in various positions at AB Hässle and Astra Hässle AB which are also presently part of the AstraZeneca organization. I have read and understood the referenced patent application. As a named inventor, I am familiar with the invention described and claimed in the referenced application. My curriculum vitae is enclosed (Exhibit A).

3. Set forth below is a summary of a clinical study performed by Astra Hässle AB on pharmaceutical formulations of omeprazole having the chemical name, 5-methoxy-2-(((4-methoxy-3, 5-dimethyl-2-pyridiny)methyl) sulfinyl)-1H-benzimidazole. As used herein, omeprazole refers to the racemic form of omeprazole.

4. The study concerns a clinical comparison of the pharmacokinetics of a multiple unit dosage form (capsule) comprising the non-salt form of omeprazole and a multiple unit tableted dosage form comprising the magnesium salt of omeprazole. The results demonstrate that the respective formulation of the capsule comprising the non-salt form of omeprazole and the multiple unit tablet comprising the magnesium salt of omeprazole are bioequivalent.

5. As described in the Example at pages 10-11 of the subject application, the pharmacological effect of the claimed method of treatment was compared with a conventional administration regimen involving omeprazole racemate. Specifically, omeprazole racemate was administered in the form of Prilosec® omeprazole capsules. A first group of subjects received Prilosec® 20 mg twice daily with 3 hours apart from administration. A second group of subjects received a single daily dose of Prilosec® 40. With each group of subjects, the efficacy of the respective administration regimen in controlling acid secretion was measured. The results showed that the therapeutic effect of omeprazole is maximized when the blood plasma concentration of the drug is extended by repeated single doses of omeprazole which are administered with 3 hours apart from each administration, when compared to a single dose. The expression "blood plasma profile" as used herein and throughout the specification of the subject application and as understood by the person of ordinary skill in the art, means the measurable concentration of the drug, i.e., the H^+,K^+-ATPase inhibitor, e.g., omeprazole, at any time subsequent to administration.

6. Applicants were requested by the Examiner during the Interview of April 10, 2001 to repeat the Example of the subject application with the multiple unit dosage form of U.S. Patent No. 5,753,265 (the "'265 patent"). The '265 patent is a cited prior art reference. A commercial product in accordance with the '265 patent is Losec® MUPS® tablets containing omeprazole magnesium salt as the active ingredient. Losec® MUPS® tablets are not currently sold in the United States. The following clinical study demonstrates that Prilosec® omeprazole capsules, i.e.,

the dosage form administered in the Example of the subject application, and Losec® MUPS® tablets of the cited '265 patent, are bioequivalent.

Clinical Study

A comparative study involving the absorption of omeprazole from separate formulations: Prilosec®, i.e., the non-salt form of omeprazole, and Losec® MUPS®, the magnesium salt of omeprazole.

The clinical study is an open, randomized, two-way cross-over trial consisting of two study periods. Each study period consisted of six days of daily oral administration of 20 mg of omeprazole or omeprazole-Mg. The pharmacokinetics (plasma levels) of the compound was studied on day 1 and day 6. Twenty-eight Caucasian subjects were included and completed the study.

Table 1: Area under the plasma concentration versus time curve (AUC; μmol x h/L) after oral administration of 20 mg of omeprazole and omeprazole-Mg, respectively.

	Day 1		Day 6	
	Omeprazole	Omeprazole-Mg	Omeprazole	Omeprazole-Mg
Geometric mean	0.84	0.86	1.48	1.56
95% Confidence interval	0.66-1.10	0.66-1.12	1.11-1.96	1.14-2.12
Coefficient of variation (%)	82.5	72.6	80.5	93.6

The results from the clinical study indicate that the same amount of substance is absorbed irrespective of the formulation administered, i.e., the non-salt form of omeprazole racemate or the Mg-salt of omeprazole racemate. Therefore, these formulations can be considered to be "bioequivalent". Furthermore, the interindividual variation, calculated as the coefficient of variation for the two formulations, is comparable.

Conclusions

The clinical study outlined above shows that Prilosec® omeprazole capsules, i.e., the dosage form administered in the Example of the subject application, and Losec® MUPS® tablets of the cited '265 patent are bioequivalent. Therefore, the unexpected advantages described in the Example of the subject application would have been obtained with Losec® MUPS® tablets of the cited '265 patent when administered twice daily with 3 hours apart, when compared to a single dose (40 mg). Accordingly, the clinical study outlined above and conclusions are fully responsive to the Examiner's request for a side-by-side comparison with the tablet dosage form of the '265 patent.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated:

Christer Cederberg, Ph.D.

CURRICULUM VITAE

Family name:	Cederberg	
Given name:	Hans Christer	
Date of birth:	18 april 1951	
Citizenship:	Swedish	
Education:	1975	B.Sc in Biology and Chemistry
	1975-79	Research student at Department of Zoophysiology, University of Gothenburg, Sweden
	1992	Doctor in Medical Science (Ph.D), Dept of Clinical Pharmacology, University of Gothenburg, Sweden
Previous positions:	1976-78	Assistant Teacher, Dept of Zoophysiology, University of Gothenburg, Sweden
	1979-81	Clinical Research Monitor, Medical Department, AB Hässle, Mölndal, Sweden
	1981-82	Clinical Research Coordinator, Medical Department , AB Hässle, Mölndal, Sweden
	1982-86	Clinical Research Manager, Medical Department, AB Hässle, Mölndal, Sweden
	1986-90	Associate Director, Gastrointestinal Clinical Pharmacology and Medicine, AB Hässle, Mölndal, Sweden
	1991-94	Associate Director, Clinical Pharmacology, Astra Hässle AB, Mölndal, Sweden
	1994-98	Scientific Adviser, Astra Hässle AB, Mölndal, Sweden
	1994-98	Project Director, Helicobacter pylori Clinical Research, Astra Hässle AB, Mölndal, Sweden
	1996-98	Member of Losec Board, Astra Hässle AB, Mölndal, Sweden
	1996-98	Chairman of Losec Working Party, Astra Hässle AB, Mölndal, Sweden
	1998-99	Director Clinical Pharmacology, Astra Research Center Boston, Cambridge, USA

Present position

1999- Director Clinical Pharmacology and Animal Science, AstraZeneca R&D Boston, Cambridge, USA

Membership:

Nordic Association for Physiology

European Association for Gastroenterology & Endoscopy

The British Society of Gastroenterology

Invited speaker to international symposia

Scandinavian workshop on regulatory mechanisms in gastric secretion - differences between animals, normal individuals and duodenal ulcer patients and implications on peptic ulcer research. Nyborg, Denmark, 18-19 august, 1981

The international Symposium on Omeprazole, Monte-Carlo, 11-12 November, 1988

Focus on gastric pump inhibitors: An update on treatment decisions in peptic ulcer disease. Toronto, Ontario, Canada 12 May, 1989

Conference on Gastrin, Dana Point, California, USA, 9-12 February 1992

Landmarks and future development in the era of acid pump inhibitors. Sidney, Australia, July, 1996

Second European Congress of Chemotherapy and 7th biannual Conference on Antiinfective Agents and Chemotherapy, Hamburg, Germany, 10-13 May, 1998

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